REMARKS

Claims 9-19 and 21 are pending.

Claim 13 has been amended to recite that the nucleic acid sequence encodes a mature phytase. The amendment is supported in the specification, for instance, in as-filed claim 1; p. 14, lines 11-19; p. 17, lines 29-34; and p. 33, lines 20-24. Withdrawn claim 17 has been amended to correct claim dependency.

New claim 21 is supported in the specification, for instance, on p. 28, lines 8-10 and p. 33, lines 20-24.

Accordingly, the amendment to the claims does not introduce new matter.

Claims 13-15 and 21 are under examination. Claims 9-12 and 16-19 are withdrawn as being directed to non-elected subject matter.

Restriction Requirement

In response to the Restriction Requirement mailed March 18, 2008, Applicants elected with traverse Group XXIII, claims 13-15 and 19. In response, the Office finalized the requirement. Claims 13-15 and 19 have been examined and rejected in the Actions dated August 20, 2008 and June 11, 2009. In the Action dated December 9, 2009, however, the Office, without explanation, held claim 19 to be withdrawn. Accordingly, Applicants seek clarification on the status of claim 19. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 68 USPQ2d 1865, 1872 (Fed. Cir. 2003) ("The restriction documentation must identify the scope of the distinct inventions that the PTO has restricted, and must do so with sufficient clarity to show that a particular claim falls within the scope of the distinct inventions.").

Rule 13.2 PCT mandates that withdrawn claims 16-19, which depend from claim 13, be rejoined and examined on the merits. PCT rules are interpreted in the PCT International Search and Preliminary Examination Guidelines, revised March 25, 2004 ("Guidelines"). Guidelines, ¶ 10.06 provides that unity of invention is "considered in the first place only in relation to the ***independent*** claims," in this case, claim 13. If the independent claim(s), i.e., claim 13, avoids the prior art, ***all*** the dependent claims, i.e., claims 14-19. have unity of invention. It does not matter if a dependent claim itself contains a further invention. Guidelines, ¶ 10.07.

Sequence Identification

The Office requested that Applicants comply with the sequence rules with regard to Figures 3 and 19-21. Specifically, the Office asserts that Figures 3 and 19-21 include sequences that lack sequence identifiers.

Applicants note that replacement figures were filed February 20, 2009 to address this issue. Specifically, in the replacement figures, the sequence in Figure 3 was identified as SEQ ID No. 1; the sequences in Figure 19 were identified as SEQ ID Nos. 12-16; the sequences in Figure 20 were identified as SEQ ID Nos. 17-23 and 32; and the sequences in Figure 21 were identified as SEQ ID Nos. 24-30 and 33.

Accordingly, Applicants believe the application already complies with the sequence rules, and in particular, with 37 C.F.R. §1.821(d).

Rejection under 35 U.S.C. § 112, 2nd paragraph

The Office has rejected claims 13-15 under 35 U.S.C. §112, 2nd paragraph as allegedly being vague and indefinite. The Office asserts that the claims could be read to recite a construct including two signal peptide sequences.

Applicants have amended the claims to make clear that the nucleic acid encodes a single signal peptide and a mature phytase, and that the nucleic acid is at least 95% identical to SEQ ID No. 2.

Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 U.S.C. § 103(a)

The Office has rejected claims 13-15 under 35 U.S.C. §103(a) as being obvious over Short et al (U.S. Pat. No. 6,720,014; "**Short**") in view of Berka et al. (U.S. Pat. No. 6,221,644; "**Berka**") and van der Laan et al. (1991, Appl Environ Microbiol. 57:901-909; "**van der Laan**").

The Office states that Short teaches a method of making variant phytases comprising error-prone amplification of a naturally occurring *E. coli* phytase nucleic acid and discloses an exemplary mature phytase sequence that is identical but for two amino acid residues to the mature sequence encoded by SEQ ID No. 2. The Office asserts that based on the

combined disclosures of Short, Berka and van der Laan, the ordinarily skilled artisan would have been motivated to use the 27 amino acid signal peptide taught by van der Laan coupled to the mature phytase taught by Short in the method taught by Short. The Office states that the proposed modification of the Short sequence with the van der Laan signal sequence results in a nucleic acid having 97% identity to SEQ ID No. 2. The Office therefore concludes the claims are obvious.

Applicants disagree.

According to the U.S. Supreme Court ruling in *Graham v. John Deere*, 383 U.S. 1 (1966), in making a *prima facie* case for obviousness, the Office must: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. These principles have been reconfirmed by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

The *KSR* court held that a combination that was "obvious to try" may indicate obviousness if there are a finite number of identified, predictable solutions and the person of ordinary skill in the art has good reason to pursue the known options within his/her technical grasp, and this pursuit leads to the anticipated success. As outlined in MPEP § 2143, to reject a claim based on an "obvious-to-try" rationale, the Office must articulate the following: 1) a finding that at the time of the invention, there had been a recognized problem or need in the art; 2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem; 3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and 4) whatever additional findings based on the *Graham* factual inquiries may be necessary. "If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." (MPEP § 2143 E*; see also Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007); *Ortho-McNeil v. Mylan Laboratories*, 520 F.3d 1358 (Fed. Cir. 2008)). Furthermore, guidance or lack thereof in directing a person of ordinary skill in the art to a particular solution must also be considered (*Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007)). The Office has failed to consider

the number of the solutions proposed in the cited art and the lack of guidance directing an ordinarily skilled artisan to the claimed invention.

Short discloses a nucleic acid sequence of an *E. coli* B phytase gene. Short generically teaches producing variants of the phytase encoded to improve the nutritional value of phytate-containing foodstuffs, including hydrolysis in the digestive tract. *See, e.g.*, col. 6, lines 40-54. Short teaches a wide variety of methods to produce variants: error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, in vivo mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, ligation reassemble, GSSM, synthetic ligation reassembly, in vivo shuffling and combinations thereof. *See, e.g.*, col. 19, line 58- col. 19, line 19; col. 23, lines 32-42; and col. 30, lines 49-62. Short teaches generically that polynucleotides may be fused to a leader sequence to control transport of a protein from a cell. *See* col. 33, lines 21-27. Short also teaches a wide variety of possible hosts for expression of a phytase gene, including: bacterial cells, such as *E. coli*, *Streptomyces*, *Bacillus subtilis*, *Salmonella typhimurium*; fungal cells, such as yeast; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9; animal cells such as CHO, COS or Bowes melanoma; adenoviruses; and plant cells. *See, e.g.*, col. 36, lines 3-10. Short does not teach any *Bacillus* signal sequences at all, let alone the composite *Bacillus* signal sequence of SEQ ID NO. 2 in the present application. Short therefore cannot and does not teach or suggest combining a *Bacillus* signal sequence with the *E. coli* B phytase gene, or use of such a nucleic acid sequence in error-prone amplification to obtain modified phytase sequences.

Berka discloses a gene encoding a polypeptide having 3,6-phytase activity that is preferably obtained from the fungi *Thermomyces*. *See, e.g.*, col. 6, lines 45-61. Berka teaches that the polypeptide can be expressed using a nucleic acid construct that can comprise a control sequence. Control sequences disclosed include: a leader, a polyadenylation sequence, a propeptide sequence, a promoter, a signal sequence and a transcription terminator, where at a minimum the nucleic acid construct contains a promoter and transcriptional and translation stop signals. Thus, Berka teaches that a signal sequence is not a necessary control sequence for expression. *See, e.g.*, col. 10, lines 15-24. Exemplary signal sequences taught by Berka can be obtained from a glucoamylase or an amylase gene from an *Aspergillus species*, a lipase or proteinase gene from a *Rhizomucor*

species, the gene for the alpha-factor from *Saccharomyces cerevisiae*, an amylase or a protease gene from a *Bacillus* species, or the calf preprochymosin gene. Regarding bacterial expression, Berka describes the following as effective signal peptides: the signal peptide coding region obtained from the maltogenic amylase gene from Bacillus NCIB 11837, the *Bacillus stearothermophilus* alpha-amylase gene, the *Bacillus licheniformis* subtilisin gene, the *Bacillus licheniformis* beta-lactamase gene, the *Bacillus stearothermophilus* neutral proteases genes (nprT, nprS, nprM), and the *Bacillus subtilis* PrsA gene. *See* col. 12, lines 32-39. Berka therefore discloses that signal sequences are optional for protein expression. Berka discloses a wide variety of signal sequences from which to chose. Berka does not, however, teach the composite *Bacillus* signal sequence of SEQ ID NO. 2 in the present application.

Van der Laan discloses the gene for a *Bacillus alcalophilus* protease. The gene encodes a serine protease having an extremely alkaline pH optimum. With regard to the 27 amino acid signal sequence of the high alkaline serine protease, van der Laan merely notes that "it is comparable to other Bacillus signal sequences." *See* p. 906, first paragraph under "Discussion." Van der Laan teaches that a homologous production system was preferred to a *B. subtilis* host. See, p. 907, first column, first paragraph. This teaching suggests that the signal sequence of the high alkaline serine protease may be ill-suited for function in a non-*Bacillus alcalophilus* host.

Short teaches a wide variety of methods for preparing variants of phytase, but does not teach the use of error-prone amplification with particularity. Furthermore, if the ordinarily skilled artisan had been motivated to modify the phytase sequence of Short to comprise a heterologous signal sequence, there were a plethora of possible signal sequences known in the art at the time of filing. Berka teaches exemplary sources of signal sequences, but does not teach *Bacillus alcalophilus* as a exemplary source, or even a possible source, of a signal sequence. Therefore, the ordinarily skilled artisan would have had numerous signal sequences to choose from and no guidance from either Short or Berka to select a signal sequence from a *Bacillus alcalophilus* high alkaline protease gene.

Furthermore, Short is directed to providing an improved phytase to use in foodstuffs for activity in the digestive system. As the ordinarily skilled artisan would know, the digestive system is an acidic milieu. Thus, the ordinarily skilled artisan would have known

that a phytase for such a system should have an acidic pH optimum. *Bacillus alcalophilus* grow at an alkaline pH of about 9 to 11.5. Thus, the ordinarily skilled artisan would not have been motivated to choose a signal sequence endogenous to *Bacillus alcalophilus*, which are obligate alkaliphiles, to use in a method of improving phytase activity for an acidic milieu. Moreover, the ordinarily skilled artisan would have viewed van der Laan's teaching regarding the homologous production system as a teaching away from the use of the high alkaline gene's signal sequence in any *Bacillus* other than *Bacillus alcalophilus*.

In summary, there are a plethora of possible solutions, both in terms of method steps and starting nucleic acid material, for preparing variants of a phytase sequence in view of Short and Berka. However, there is no specific guidance leading the ordinarily skilled artisan to use a signal sequence from a *Bacillus alcalophilus* protease, such as that disclosed by van der Laan, with the *E. coli* phytase sequence taught by Short. Accordingly, there were a great many possible solutions known to the ordinarily skilled artisan, and no specific guidance leading the ordinarily skilled artisan to the claimed method. As such, the Office's obvious-to-try rationale cannot be used to support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

Reconsideration and withdrawal of the rejection is requested.

SUMMARY

Applicants respectfully submit that the rejections by the Office to the claims of the present application have been overcome, and that claims 13-15 are now in condition for allowance. Upon allowance of claim 13, rejoinder and examination of currently-withdrawn claim 16-19 is requested. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date. The undersigned representative signs in her capacity under 37 C.F.R. § 1.34.

Respectfully submitted,

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Date

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